REMARKS

I. Comments on Restriction Requirement

Applicants reiterate their arguments presented in the response filed November 2, 2001, concerning the improper restriction requirement between the various SEQ ID NOs recited by the claims. In addition, Claims 12-14, 23, 26, 27, and 29, as well as new Claims 32-36, are method of use claims which ultimately depend from independent product Claims 3, 10, and 31. Therefore, upon allowance of Claims 3, 10, and 31, it is believed that Claims 12-14, 23, 26, 27, 29, and 32-36 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)."

II. Objections to the Specification

A. Priority Claim

The Examiner objected to the Specification, stating that "Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78)." (Office Action, page 4.)

Applicants have amended the Specification to add the following as the first sentence in the Specification: "This application claims benefit under 35 U.S.C. § 119(e) of Provisional Application No. 60/124,655, filed March 16, 1999."

B. Title

The Examiner objected to the title of the patent application, stating that "[t]he title of the invention is not descriptive." (Office Action, page 4.) The Examiner suggested the title "Isolated nucleic acid molecule encoding a human NADH-ubiquinone oxidoreductase."

Applicants have amended the application title to "ISOLATED POLYNUCLEOTIDE

ENCODING A HUMAN PSST SUBUNIT OF THE NADH:UBIQUINONE OXIDOREDUCTASE COMPLEX."

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the objections to the Specification.

III. Objections to the Claims

The Examiner objected to Claims 3, 8, 24, and 28 "under 37 CFR 1.75(c) as being in improper form because these claims depend on non-elected claims." (Office Action, page 4.) Applicants have amended Claims 3, 8, 24, and 28 so that they do not depend from non-elected claims. Therefore, Applicants respectfully request that the Examiner withdraw the objection to the claims.

IV. Rejection of Claims 3, 8, 10, and 30 Under 35 U.S.C. §112, second paragraph

The Examiner rejected Claims 3, 8, 10, and 30 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Office Action, page 6.)

A. Claims 3 and 8

The Examiner rejected Claims 3 and 8 for reciting "biologically active fragment," alleging that "[t]his term,. . . renders the claim vague and unclear because applicant's definition does not clarify which functions of the protein of SEQ ID NO:1 are encompassed by the definition" and that "the term 'fragment' renders the claim vague and confusing because the size of a fragment has not been defined in the claim or in the specification." (Office Action, page 6.)

In order to expedite prosecution, amended Claim 3 does not recite polynucleotides encoding biologically active fragments of SEQ ID NO:1.

B. Claims 10(c) and 10(d)

The Examiner rejected Claims 10(c) and 10(d), alleging that the phrase "a polynucleotide sequence complementary to" is indefinite. The Examiner suggested that "Applicants clarify their

meaning of the term complementary by replacing the term 'a polynucleotide sequence complementary to' with, for example, 'a polynucleotide sequence completely complementary to.'" (Office Action, page 7.)

Amended Claim 10, and new Claim 31, adopt the changes suggested by the Examiner.

C. Claim 30

The Examiner rejected Claim 30, alleging that "it is unclear what the term 'first' refers to" and that "the term 'specifically hybridizable' is unclear absent a statement indicating the conditions under which the hybridization/wash reaction takes place." (Office Action, page 7.)

In order to expedite prosecution, Claim 30 is amended to:

> An array comprising different nucleotide molecules affixed in distinct physical locations on a solid substrate, wherein at least one of said nucleotide molecules comprises an oligonucleotide or polynucleotide sequence completely complementary to at least 30 contiguous nucleotides of a target polynucleotide, and wherein said target polynucleotide is a polynucleotide of claim 10.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the indefiniteness rejection of Claims 3, 8, 10, and 30.

V. Rejection of Claim 3 Under 35 U.S.C. §112, first paragraph, enablement

The Examiner rejected Claim 3 under 35 U.S.C. §112, first paragraph, alleging that the claimed polynucleotides encoding a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and polynucleotides encoding fragments of SEQ ID NO:1 were not enabled.

In order to expedite prosecution, amended Claim 3 does not recite polynucleotides encoding fragments of SEQ ID NO:1 or encoding polypeptides having at least 90% sequence identity to SEQ ID NO:1. Therefore, this rejection is moot.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the enablement rejection of Claim 3.

VI. Rejection of Claim 10 Under 35 U.S.C. §112, first paragraph, enablement

The Examiner rejected Claim 10 under 35 U.S.C. §112, first paragraph, alleging that the claimed polynucleotides comprising a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence of SEQ ID NO:9 are not enabled.

New Claim 31 recites polynucleotides comprising a naturally occurring polynucleotide sequence having at least 80% sequence identity to a polynucleotide sequence of SEQ ID NO:9. Claim 10 does not recite polynucleotides comprising a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence of SEQ ID NO:9, and therefore this rejection as it applies to Claim 10 is moot. Therefore, this rejection is addressed as far as it applies to new Claim 31.

The claimed polynucleotides are enabled, i.e., they are supported by the Specification and what is well known in the art.

A. How to make

SEQ ID NO:1 and SEQ ID NO:9 are specifically disclosed in the application (see, for example, pages 1, 6, and 7 of the Sequence Listing). Variants of SEQ ID NO:1 and SEQ ID NO:9 are described, for example, on page 18, line 28 through page 19, line 15, page 20, lines 29-32, and page 21, lines 4-12. Incyte clones in which the nucleic acids encoding the human MITP-1 were first identified and libraries from which those clones were isolated are described, for example, in Tables 1, 3, and 4. Chemical and structural features of MITP-1 are described, for example, in Table 2. "Naturally occurring" polynucleotide sequences occur in nature; they are not created exclusively in a laboratory. The Specification describes how to find naturally occurring analogs and homologs in other individuals and species (e.g., page 39, lines 3-6) and how to use CLUSTAL V and BLAST to determine whether a given naturally occurring polynucleotide sequence falls within the "having at least 80% sequence identity to a polynucleotide sequence of SEQ ID NO:9" scope (e.g., page 11, line 22 through page 12, line 32). The making of the claimed polynucleotides by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 21, lines 31-35, page 24, lines 14-16,

and page 34, lines 24-31. This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

B. How to use

The specification discloses numerous practical, beneficial uses for the claimed polynucleotide variants, for example, in toxicology testing, drug development, and the diagnosis of disease (Specification, e.g., at page 38, line 25 through page 41, line 24, and page 48, line 18 through page 49, line 2). These uses are well-established in the art. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Likewise, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. Polypeptide or polypeptide fragments known to be expressed are tools essential to any technology that uses proteome expression profiling. See, *e.g.*, Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000) (Reference No. 1).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (1999) (Reference No. 2):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new

drugs. (Reference No. 2, page 656.)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 3); Sandra Steiner and N. Leigh Anderson, *supra*.

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip. (Reference No. 3, page 156.)

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999) (Reference No. 4, see page 683). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 5), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. This is true for both polynucleotides and polypeptides encoded by them.

There are numerous additional uses for the information made possible by expression profiling.

Expression profiling is used to identify drug targets and characterize disease. See Rockett et al., *supra*. It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical, substantial and credible real-world utilities, at the very least for expression profiling.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression.

There is simply no doubt that the sequences of expressed human polynucleotides and polypeptides all have practical, substantial and credible real-world uses, at the very least for biochemical pathway elucidation, drug target identification, and assessment of toxicity and treatment efficacy in the drug development process. This use applies to all expressed sequences and therefore to all polynucleotide sequences of Claims 10 and 31. Sandra Steiner and N. Leigh Anderson, *supra*, have elaborated on this topic as follows:

> The rapid progress in genomics and proteomics technologies creates a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process. Application of gene and protein expression profiling promises to improve lead selection, resulting in the development of drug candidates with higher efficacy and lower toxicity. The identification of biologically relevant surrogate markers correlated with treatment efficacy and safety bears a great potential to optimize the monitoring of pre-clinical and clinical trials. (Reference No. 1, page 470.)

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the

power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the enablement rejection of Claim 10, and as it may apply to new Claim 31.

VII. Rejection of Claims 11, 28, and 30 Under 35 U.S.C. §112, first paragraph, enablement

The Examiner rejected Claims 11, 28, and 30 under 35 U.S.C. §112, first paragraph, alleging that the claimed polynucleotide fragments and microarrays containing said fragments were not enabled. In order to expedite prosecution, Claims 11, 28, and 30 do not recite polynucleotide fragments of SEQ ID NO:9 or microarrays containing said fragments. Therefore, the rejection as it pertains to Claims 11, 28, and 30 is moot.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the enablement rejection of Claims 11, 28, and 30.

VIII. Rejection of Claims 3, 5, 6, 10, and 11 Under 35 U.S.C. §102(b) as Anticipated by Hyslop

The Examiner rejected Claims 3, 5, 6, 10, and 11 under 35 U.S.C. §102(b) as being anticipated by Hyslop et al. (Genomics 37:375:380, 1996).

In order to expedite prosecution, Claims 3 and 10 were amended and Claim 31 was added. Amended Claim 3 does not recite polynucleotides encoding fragments of SEQ ID NO:1 or encoding polypeptides having at least 90% sequence identity to SEQ ID NO:1. Amended Claim 10, and Claim 11, which depends from Claim 10, do not recite SEQ ID NO:9. New Claim 31 recites:

An isolated polynucleotide selected from the group consisting of:
a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:9,
b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9,
c) a polynucleotide completely complementary to a polynucleotide of a),
d) a polynucleotide completely complementary to a polynucleotide of b), and
e) an RNA equivalent of a)-d).

Hyslop does not recite the polypeptide sequence of SEQ ID NO:1, the polynucleotide sequence of SEQ ID NO:9 or a naturally occurring polynucleotide sequence having at least 80% sequence identity to a polynucleotide sequence of SEQ ID NO:9. Therefore Hyslop does not anticipate Claims 3, 5, 6, 10, 11, and 31. A naturally occurring polynucleotide sequence having at least 80% sequence identity to a polynucleotide sequence of SEQ ID NO:9 is supported in the Specification, e.g., at page 18, lines 31-33.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the prior art rejections over Hyslop.

IX. Rejection of Claims 3, 5, and 6 Under 35 U.S.C. §102(b) as Anticipated by Arizmendi

The Examiner rejected Claims 3, 5, and 6 under 35 U.S.C. §102(b) as being anticipated by Arizmendi et al., (FEBS Lett. 301:237-242, 1992; Swiss Prot accession number P42026, November 1, 1995).

In order to expedite prosecution, Claim 3 as amended does not recite polynucleotides encoding fragments of SEQ ID NO:1. Arizmendi does not recite the polypeptide sequence of SEQ ID NO:1 or polynucleotides encoding the polypeptide sequence of SEQ ID NO:1. Therefore Arizmendi does not anticipate Claims 3, 5, and 6.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the prior art rejection of Claims 3, 5, and 6 over Arizmendi.

X. Rejection of Claim 8 Under 35 U.S.C. §103(a) as Being Unpatentable Over Hyslop

The Examiner rejected Claim 8 under 35 U.S.C. §103(a) as being unpatentable over Hyslop et al. (Genomics 37:375:380, 1996).

In order to expedite prosecution, Claim 8 has been amended to depend from Claim 3. Amended Claim 3 does not recite polynucleotides encoding fragments of SEQ ID NO:1 or encoding polypeptides having at least 90% sequence identity to SEQ ID NO:1. Therefore Hyslop does not render Claim 8 obvious.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the obviousness rejection of Claim 8 over Hyslop.

XI. Rejection of Claims 28 and 30 Under 35 U.S.C. §103(a) as Being Unpatentable Over Hyslop

The Examiner rejected Claims 28 and 30 under 35 U.S.C. §103(a) as being unpatentable over Hyslop et al. (Genomics 37:375:380, 1996).

In order to expedite prosecution, Claims 28 and 30, which depend directly or indirectly from Claim 10, do not recite fragments of SEQ ID NO:9.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the obviousness rejection of Claims 28 and 30 over Hyslop.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections and rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent at (650) 854-4646.

Please charge Deposit Account No. **09-0108** in the amount of $ 18.00 as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. **09-0108.**

Respectfully submitted,

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Date: June 12, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE TITLE:

The title has been amended as follows:

ISOLATED POLYNUCLEOTIDE ENCODING A HUMAN PSST SUBUNIT OF THE NADH:UBIQUINONE OXIDOREDUCTASE COMPLEX [MITOCHONDRIAL PROTEINS]

IN THE SPECIFICATION:

The following sentence was added immediately after the title of the application on page 1 of the Specification:

This application claims benefit under 35 U.S.C. § 119(e) of Provisional Application No. 60/124,655, filed March 16, 1999.

IN THE CLAIMS:

Claims 1, 2, 7, 9, and 15 have been canceled.

Claims 31-36 have been added.

Claims 3, 8, 10, 24, 28, and 30 have been amended as follows:

3. (Once Amended) An isolated polynucleotide encoding a polypeptide [of claim 1] selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-8,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2-8, and

c) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:2-8.

8. (Once Amended) A method for producing a polypeptide [of claim 1] encoded by the polynucleotide of claim 3, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide of claim 3 [encoding the polypeptide of claim 1], and

b) recovering the polypeptide so expressed.

10. (Once Amended) An isolated polynucleotide [comprising a polynucleotide sequence] selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:10-16 [9-16],

b) a polynucleotide comprising a naturally occurring polynucleotide sequence [having] at least 70% [sequence identity] identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:10-16 [9-16],

c) a polynucleotide [sequence] completely complementary to a polynucleotide of a),

d) a polynucleotide [sequence] completely complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

24. (Once Amended) An isolated polynucleotide [encoding] of claim 3 which encodes a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-8 [of claim 2].

28. (Once Amended) A microarray wherein at least one element of the microarray is a polynucleotide of claim 11 [14].

30. (Once Amended) An array comprising different nucleotide molecules affixed in distinct physical locations on a solid substrate, wherein at least one of said nucleotide molecules comprises an

[a first] oligonucleotide or polynucleotide sequence completely complementary to [specifically hybridizable with] at least 30 contiguous nucleotides of a target polynucleotide, and wherein said target polynucleotide is a polynucleotide of claim 10.